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(54) Title: USE OF CSAID™ COMPOUNDS FOR THE MANAGEMENT OF UTERINE CONTRACTIONS

(57) Abstract

The present invention is to the novel use of a cytokine inhibitor for the prophylactic treatment, or management of excessive, undesired or inappropriate uterine activity, such as contractions, in a mammal in need thereof.

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Use of CSAID™ Compounds for the Management of Uterine Contractions

FIELD OF THE INVENTION

The present invention relates to the treatment of inappropriate, excessive or undesirable uterine contractions, in a mammal.

BACKGROUND OF THE INVENTION

Preterm labour is of major concern to both obstetricians and neonatologists. It affects approximately 10% of pregnancies and results in 30% of long term neonatal handicap and 85% of perinatal deaths. The pathogenesis of preterm labour is incompletely understood at present, it is therefore difficult to both predict and treat effectively. The underlying biochemical pathways involved in the initiation of parturition have not yet been fully elucidated. There are clear links between inflammatory processes and activation of the immune system in the maternal decidua. Prostaglandins, which have a well documented role in the initiation of labour, (Mitchell, MD., (1984) *Journal of Developmental Physiology,* **6**, 107-118) and the inflammatory cytokines (Mitchell, MD., et al. (1993) *Clinical Obs. and Gynaecol,* **3**, 553-575) have therefore both been implicated in the pathogenesis of labour. Interleukin-1β (IL-1β) has been demonstrated to be the pivotal cytokine in the biochemical pathway leading to labour (Mitchell, MD., et al.(1993), *supra*). It has been shown to directly stimulate the production of prostaglandins which are the terminal products of the inflammatory response and direct initiators of labour (Romero, R., et al. (1992) *Am. J. Reprod. Immunol,* **33**, 117-123; and Kent A.S.H., et al. (1993) *Prostaglandins* **46**, 51-59). Levels of IL-1β have been shown to rise following stimulation with bacterial endotoxin (Romero, R., et al. (1989) *Am. J. Obstet and Gynaecol.*, **160**, 1117) which implies a mediating role for this cytokine in the induction of labour in the presence of infection.

The production of prostaglandins is under the influence of two enzymes, phospholipase A2 and cyclo-oxygenase (COX) alternatively known as prostaglandin H synthase. COX has been found to be present in two forms; type-1 COX is the constitutive form of the enzyme present in all tissues. Type-2 COX is the inducible form of the enzyme that has been shown to be up-regulated near term (Macchia L., et al. (1997) *Biochemical and Biophysical Research*

Communications, **233**, 496-501). IL-1β is able to increase the production of COX-2 in amnion (Trautman M.S., et al. (1996) *Placenta*, **17**, 239-245).

By modulating the production of prostaglandin E_2 (PGE_2) the contractile activity of the uterus may be controlled. Tocolytic agents that completely suppress contractions are not yet available. There has been very little recent progress in the therapeutic modalities available to treat preterm labour. Currently a therapeutic cocktail consisting of betasypathomimetics, Non-Steroidal Anti-inflammatory Drugs (NSAID's), and oxytocin antagonists is used to try and suppress unwanted uterine activity.

The therapeutic cocktail does not fully address the management of preterm labor in patients, therefore a need still exists to find suitable small molecule inhibitors which will help modulate the contactile activity of the uterus in a mammal in need thereof.

SUMMARY OF THE INVENTION

The present invention is to the novel use of a cytokine inhibitor for the prophylatic treatment or management of excessive, undesired or inappropriate uterine activity in a mammal, which method comprises administering to said mammal an effective amount of a compound which inhibits the production, transcription or translation of a cytokine. Preferably, the cytokine is inhibited by inhibition of the kinase CSBP/p38/RK.

The preferred compounds for use as cytokine inhibitors are those compounds of Formula (I) as noted herein. The preferred method of inhibition is the inhibition of the CSBP/p38/RK kinase pathway.

DETAILED DESCRIPTION OF THE INVENTION

The current application teaches the novel finding that CSAID™ compounds, i.e. compounds that block cytokine production, can be a therapeuticially effective agent in modulating uterine contractile activity. Such modulation will help treat preterm labour in patients in need thereof.

The present invention is to the novel use of a cytokine inhibitor, in particular that of cytokine CSBP/p38, for the prophylactic treatment or management of excessive, undesired or inappropriate uterine activity in a mammal.

As noted above, by modulating the production of prostaglandin E_2 (PGE_2) the contractile activity of the uterus may be controlled. Tocolytic agents

that completely suppress contractions are not yet available and there has been very little recent progress in the therapeutic modalities available to treat preterm labour. The current treatment for preterm labour is a therapeutic cocktail consisting of betasypathomimetics, Non-Steroidal Anti-inflammatory Drugs (NSAID's), and oxytocin antagonists. This cocktail is used to try and suppress unwanted uterine activity.

PGE_2 production by fetal membranes has been shown to be inhibited by the use of NSAID's. The efficacy in controlling uterine activity is however dependent on the specificity of the agent used and the treatments are not without their side-effects. It has now been found that small molecule inhibitors which act on cytokine synthesis may also have a similar inhibitory effect on the production PGE_2 by inhibiting cytokine driven prostaglandin production and could therefore be useful in the treatment and prevention of preterm labour. Therefore, another aspect of the present invention is the use of cytokine inhibitors of the p38/CSPB/RK pathway in the treatment of both preterm and term labour.

As will be demonstrated herein in the Example section, the CSAID™ compound SKF86002 has effectively been used to modulate prostaglandin and interleukin production from gestational tissues. The compound SKF 86002 has previously been shown to decrease the production of IL-1β from lipopolysaccharide (LPS) stimulated isolated human macrophages (Perregaux D. G., et al. (1995) *Molecular pharmacology*, **48**, 433-442) and the production of prostaglandin H synthase from rat basophilic leukaemic cells (Griswold D.E., et al. (1987) *Biochemical Pharmacology*, **36**, 3463-3470).

The term "inappropriate uterine activity "as used herein includes, but is not limited to, diseases which are characterized by the presence of unwanted or excessive uterine activity prior to the completion of normal gestational period in a mammal. In the case of a human, for instance, this would be approximately a 40 week gestation.

The term "excessive or increased uterine activity" as used herein is characterized by the presence of abnormal uterine action during labour. Abnormal uterine action during labour is characterized by the excessive frequency, amplitude or duration of uterine contractions.

The term "pre-term labour" as used herein refers to the onset of labour before 37 weeks gestation. However, it is recognized that pre-term labour is a complex syndrome due

to many aetiological factors. See for instance, Romero, et al., Ann NY Acad. Sci., 734, page 414 (1994).

Labour and pre-term labour are characterized by the presence of 1) sustained uterine contractions; 2) dilatation of the cervix; and 3) rupture of the fetal membranes

All three components of labour are mediated in part by the action of inflammatory cytokines, consequently use of a CSBP inhibitor would be of use in all these areas.

In particular, dilatation, or ripening of the cervix is affected by the reorganization of collagen bundles in the cervix. This is believed to be under the control of the enzyme collagenase, produced by neutrophils (Osmers, et al., American Journal of Obstetrics & Gynecology, 166, pp 1455-1460 (1992)). Neutrophils migrate into the cervix from the surrounding tissues under the influence of chemotactic inflammatory cytokines such as IL-8. They are then stimulated by IL-8 to release collagenase which breaks down the collagen bundles in the cervix. IL-8 has also been shown to soften the cervix after topical application. See, Chwalisz, et al., Human Reproduction, 9, pp 2173-2181 (1994); and El Maradny et al., American Journal of Obstetrics & Gynecology, 171, pp 77-83 (1994). Therefore, use of a CSBP inhibitor should inhibit unwanted cervical ripening in a mammal.

In preterm rupture of the fetal membrane (PROM) there is significant evidence which implicates infection and inflammation in the pathogenesis of fetal membrane rupture (French et al., Seminars in Perinatology, 20 pp 344-368 (1996)). Proteases produced in response to infection have been shown to be involved in a reduction in fetal membrane tensile strength (McGregor, et al., Obstet and Gynceol, 69, pp 167-174 (1987)). These proteases are under the influence of inflammatory cytokines such as IL-1α and IL-1β, and TNF-α (Woessner, J. FASEB J, 5, pp 2145-2154 (1991). An inhibitor of these cytokines, such as CSAID™ inhibitor, would therefore be able to prevent the unwanted rupture of the fetal membranes by preventing the release of inflammatory cytokines which stimulate the release of proteases, etc., which in turn destroy the integrity of the fetal membranes.

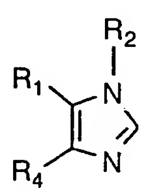
Eclampsia and pre-eclampsia are thought to result from the defective penetration of maternal blood vessels (the spiral arteries) into the trophoblast. Inflammatory cytokines are important in mediating this process. Many studies have implicated a variety of cytokine in the pathogenesis of pre-eclampsia. IL-4 has been shown to be elevated in the sera of pre-eclamptic women (Omu-Ae et

al., Nutrition, 11(5Suppl), pp 688-91 (1995 -Sep-Oct). Thus, pre-eclampsia/ intrauterine dystrophy is characterized by reduction of some cytokines within the amniotic fluid compartment and concomitant reactive augmentations of other cytokines within the maternal and fetal organism. Stallmach et al., Reprod-Fertil-Dev. 1995; 7(6): 1573-80 (1995). IL-6 levels have also been shown to be increased in pre-eclamptic patients (Greer et al., Obstet-Gynecol., 84(6) (1994). A CSAID™ inhibitor, may therefore favourably modify the cytokine profile in pre-eclamptic and eclamptic patients by decreasing the severity of the disease.

Other cytokine inhibitory compounds for use in the present invention include, but are not limited to, those described in USSN 08/091,491, published as WO95/02575; WO95/02591; US 5,593,992; US 5,663,334; US 5,670,527; WO96/21452; WO96/21654; US 5,658,903 and WO96/40143; US 5,739,143; WO96/21654; WO93/14081; US Patent 5,656,644; USSN 08/095,234; US 5,686,455; US 5,559,137; US 5,656,644 and WO95/03297; USSN 08/481,671; WO97/25048; WO97/25047; US 5,756,499 and WO97/25045; US 5,716,955 and WO97/25046; WO97/33883; WO92/10190; WO92/10498; WO98/06715; WO93/14082; WO95/13067; WO95/31451; WO 98/07425; PCT/US98/12387; WO97/05877; PCT/US98/12828; PCT/US98/13808; PCT/US97/23638; USSN 60/068,178; USSN 60/061351; WO92/12154; EP 0531901; US 5,670,503 and WO94/19350; WO97/05878; WO97/05877; WO97/05878; WO97/16441; WO97/16426; WO97/12876; US 5,717,100; WO97/45412; WO97/36587; and WO97/16442. Each of these references are incorporated by reference herein in their entirety.

Preferred compounds for use as cytokine inhibitors are those compounds of Formula (I) as noted herein. Synthetic chemistry and methods of pharmaceutical formulations thereof are also contained within each noted patent application. A description of the assay for inhibition of the cytokine specific binding protein (CSBP) is also found in WO95/07922, whose disclosure is incorporated by reference in its entirety.

A preferred group of compounds for use herein are those compounds of the formula (I):


(I)

wherein:

R_1 is a pyrid-4-yl, pyrimidin-4-yl, pyridazin-4-yl, 1,2,4-triazin-5-yl, quinol-4-yl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl ring, which ring is optionally substituted independently one to three times with Y, NHR_a, optionally substituted C_{1-4} alkyl, halogen, hydroxyl, optionally substituted C_{1-4} alkoxy, optionally substituted C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or $N(R_{10})C(O)R_b$;

Y is $O\text{-}R_a$;

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $C(Z)NR_7R_{17}$, $C(Z)OR_{16}$, $(CR_{10}R_{20})_vCOR_{12}$, SR_5, SOR_5, OR_{12}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $ZC(Z)R_{12}$, $NR_{10}C(Z)R_{16}$, or $(CR_{10}R_{20})_vNR_{10}R_{20}$, and which, for other positions of substitution, is halogen, cyano, $C(Z)NR_{13}R_{14}$, $C(Z)OR_3$, $(CR_{10}R_{20})_{m''}COR_3$, $S(O)_mR_3$, OR_3, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_3$, $NR_{10}S(O)_{m'}R_8$, $NR_{10}S(O)_{m'}NR_7R_{17}$, $ZC(Z)R_3$ or $(CR_{10}R_{20})_{m''}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

m is 0, or an integer having a value of 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is hydrogen, $(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenylC_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, cycloalkyl, cycloalkylalkyl,

heteroaryl, heteroaryl alkyl, heterocyclyl and heterocyclyl alkyl groups may be optionally substituted;

Z is oxygen or sulfur;

R_a is a C_{1-6} alkyl, aryl, arylC_{1-6} alkyl, heterocyclyl, heterocyclylC_{1-6} alkyl, heteroaryl, or heteroarylC_{1-6} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties SR_5 being SNR_7R_{17} and SOR_5 being SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is a C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, or $(CR_{10}R_{20})_nNR_{13}R_{14}$ moiety; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl moieties may be optionally substituted;

R_9 is hydrogen, $C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted arylC_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen and C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclylC_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl and optionally substituted arylC_{1-4} alkyl; or together with the nitrogen to which they are attached R_{13} and R_{14} form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylC_{1-10} alkyl, heterocyclyl, heterocyclylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;
R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;
or a pharmaceutically acceptable salt thereof.

Suitably, R_1 is a substituted 4-pyridyl or 4-pyrimindyl. More suitably R_1 is substituted by an optionally substituted alkoxy, alkylthio, amino, methylamino, NHRa, or Y. A preferred ring placement of the R_1 substituent on the 4-pyridyl derivative is the 2-position, such as in 2-methoxy-4-pyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, such as in 2-methoxy-pyrimidinyl.

Suitably, R_a is a C_{1-6} alkyl, aryl, arylC_{1-6} alkyl, heterocyclyl, heterocyclylC_{1-6} alkyl, heteroaryl, or heteroarylC_{1-6} alkyl moiety, wherein each of these moieties may be optionally substituted.

When the substituent is Y, and R_a is aryl, it is preferably an optionally substituted phenyl or naphthyl. When R_a is an arylalkyl, it is preferably an optionally substituted benzyl or naphthylmethyl. When R_a is a heterocyclyl or heterocyclyl alkyl moiety, the heterocyclic portion is preferably an optionally substituted ring which is pyrrolindinyl, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyranyl, tetrahydrothipyran-sulfinyl, tetrahydrothio-pyransulfonyl, pyrrolindinyl, indole, or piperonyl. It is noted that the heterocyclic rings herein may contain unsaturation, such as in a tryptamine ring.

The R_a moieties, in particular the aryl, may be optionally substituted, preferably 1 to 3 times, independently with halogen; C_{1-4} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF_3; hydroxy; hydroxy substituted C_{1-4} alkyl; C_{1-4} alkoxy, such as methoxy or ethoxy; $S(O)_m$alkyl and S(O)m aryl (wherein m is 0, 1, or 2); $C(O)OR_{11}$, such as $C(O)C_{1-4}$ alkyl or C(O)OH moieties; $C(O)R_{11}$; $OC(O)R_c$; -O-(CH_2)s-O-, such as in a ketal or dioxyalkylene bridge; amino; mono- and di-C_{1-6} alkylsubstituted amino; $N(R_{10})C(O)R_b$; $C(O)NR_{10}R_{20}$; cyano; nitro; or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15}; optionally substituted aryl, such as phenyl; optionally substituted arylalkyl, such as benzyl or phenethyl; optionally substituted aryloxy, such as phenoxy; or optionally substituted arylalkyloxy such as benzyloxy. The aryl, arylalkyl, aryloxy, or arylalkyloxy optional substituents are as defined in the "optional substituent" definition herein.

Suitably, R_c is an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted arylC_{1-4} alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4} alkyl, optionally substituted

heterocyclyl, or optionally substituted heterocyclylC_{1-4} alkyl moieties; and wherein the optional substituents are as defined in the "optional substituent" definition herein.

Preferably, the R_a groups include C_{1-4} alkyl, benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, aminocarbonylphenyl, alkylphenyl, cyanophenyl, alkylthiophenyl, hydroxyphenyl, alkoxyphenyl, morpholinopropyl, piperonyl, piperidin-4-yl, alkyl substituted piperidine, such as 1-methylpiperidine, or 2,2,6,6-tetramethylpiperidin-4-yl.

Preferably, when the substituent is NHR_a then R_a is aryl, arylalkyl, halosubstituted arylalkyl, halosubstituted aryl, heterocyclyl alkyl, hydroxy alkyl, alkyl-1-piperidine-carboxylate, heterocyclyl, alkyl substituted heterocyclyl, halosubstituted heterocyclyl, or aryl substituted heterocyclyl. More preferably, R_a is benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, morpholinopropyl, 2-hydroxy ethyl, ethyl-1-piperidinecarboxylate, piperonyl, piperidin-4-yl, alkyl substituted piperidine, chlorotryptamine, or tetrathiohydropyranyl.

Preferably, when the R_1 substituent is an optionally substituted C_{1-4} alkoxy or C_{1-4} alkylthio, it is preferably a methoxy group. If the alkyl chain in these moieties is optionally substituted it is preferably substituted by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy, such as hydroxyethoxy; C_{1-10} alkoxy, such as a methoxymethoxy, S(O)m alkyl, wherein m is 0, 1 or 2; amino, mono and di-substituted amino, such as in the NR_7R_{17} group, i.e. tert-butylaminoethoxy; or where the R_7R_{17} may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; or halosubstituted C_{1-10} alkyl, such as CF_3.

Suitably, R_4 is an optionally substituted phenyl. Preferably the phenyl is substituted one or more times independently by halogen, SR_5, $S(O)R_5$, OR_{12}, halo-substituted-C_{1-4} alkyl, or C_{1-4} alkyl, preferably in the 4-position of the ring. More preferably R_4 is a halosubstituted phenyl, more preferably in the 4-position; and most preferably by fluorine.

Suitably, R_2 is hydrogen, $(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenylC_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$,

$(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl group, and wherein the aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryl alkyl, heterocyclyl and heterocyclyl alkyl groups may be optionally substituted.

Suitably, R_2 is hydrogen, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-10} alkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-7} cycloalkylC_{1-10} alkyl, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, optionally substituted aryl, optionally substituted arylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, or $(CR_{10}R_{20})_nC$ $(=NOR_6)R_{11}$.

More suitably, R_2 is selected from hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nNS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, aryl$C_{1-10}$ alkyl, $(CR_{10}R_{20})_nNR_{13}R_{14}$, optionally substituted C_{3-7} cycloalkyl, or optionally substituted C_{3-7} cycloalkylC_{1-10} alkyl.

Preferably R_2 is hydrogen, morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-aminopiperidine, 4-amino-2,2,6,6-tetramethylpiperidine, 4-hydroxycyclohexyl, 4-methyl-4-hydroxycyclohexyl, 4-pyrrolinindylcyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-ketocyclohexyl, 4-oxiranyl, or 4-hydroxy-4-(1-propynyl)cyclohexyl.

More preferably R_2 is an optionally substituted heterocyclyl ring, optionally substituted heterocyclylC_{1-10} alkyl, optionally substituted aryl, $(CR_{10}R_{20})_nNR_{13}R_{14}$, or $(CR_{10}R_{20})_nC(Z)OR_{11}$ group. Most preferably an optionally substituted heterocyclyl ring, or optionally substituted heterocyclylC_{1-10} alkyl.

When R_2 is optionally substituted heterocyclyl, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. When the ring is optionally substituted, the substituents may be directly attached to the free nitrogen, such as in the piperidinyl group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. The heterocyclyl ring may be optionally substituted one to four times independently by halogen; C_{1-4} alkyl; aryl, such as phenyl; aryl alkyl, such as benzyl - wherein the aryl or aryl alkyl moieties themselves may be optionally substituted (as in the "optionally substituted" definition below); $C(O)OR_{11}$, such as the $C(O)C_{1-4}$ alkyl or $C(O)OH$ moieties; $C(O)H$; $C(O)C_{1-4}$ alkyl; hydroxy substituted C_{1-4} alkyl; C_{1-4} alkoxy;

$S(O)_mC_{1-4}$ alkyl (wherein m is 0, 1, or 2); and $NR_{10}R_{20}$ (wherein R_{10} and R_{20} are independently hydrogen or C_{1-4}alkyl).

Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i.e. a 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, or 1-ethoxycarbonyl-4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2- or 6- position or both, such as 2,2,6,6-tetramethyl-4-piperidine. Similarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are all directly on the available nitrogen.

When R_2 is an optionally substituted heterocyclylC_{1-10} alkyl group, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. Preferably the alkyl linking moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3 carbons, such as in a propyl group. Preferred heterocyclyl alkyl groups include but are not limited to, morpholino ethyl, morpholino propyl, pyrrolidinyl propyl, and piperidinyl propyl moieties. The heterocyclic ring herein is also optionally substituted in a similar manner to that indicated above for the direct attachment of the heterocyclyl ring.

When R_2 is an optionally substituted C_{3-7} cycloalkyl, or an optionally substituted C_{3-7} cycloalkylC_{1-10} alkyl, the cycloalkyl group is preferably a C_4 or C_6 ring, most preferably a C_6 ring, which ring is optionally substituted.

The cycloalkyl ring may be optionally substituted one to three times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_m$ alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; $S(O)_m$ aryl; cyano; nitro; amino; mono and di-C_{1-10} alkyl substituted amino, such as in the NR_7R_{17} group, wherein R_7 and R_{17} are as defined in Formula (I), or where the R_7R_{17} may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from oxygen, sulfur or NR_{15}; $N(R_{10})C(O)X_1$, wherein X_1 is C_{1-4} alkyl, aryl or arylC_{1-4} alkyl; C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; optionally substituted alkyl wherein the substituents are halogen, (such as CF_3), hydroxy, nitro, cyano, amino, mono & di-C_{1-10} alkyl substituted amino; NR_7R_{17}; S(O)m alkyl and S(O)m aryl, wherein m is 0, 1 or 2; optionally substituted alkylene, such as ethylene or propylene; optionally substituted alkyne, such as ethyne; $C(O)OR_{11}$; the group R_e; C(O)H; =O; $=N-OR_{11}$; N(H)-OH (or substituted alkyl or aryl derivatives thereof on the nitrogen or the oxime moiety); $N(OR_d)-C(O)-R_{6'}$; an optionally substituted aryl, such as phenyl; an optionally substituted arylC_{1-4} alkyl, such as benzyl or phenethyl; an optionally substituted heterocyclyl or heterocyclylC_{1-4} alkyl, and further wherein these aryl,

arylalkyl, heterocyclyl, and heterocyclyl alkyl moieties are optionally substituted one to two times by halogen, hydroxy, C_{1-10} alkoxy, $S(O)_m$ alkyl, cyano, nitro, amino, mono and di-C_{1-10} alkyl substituted amino, alkyl, or halosubstituted alkyl.

Suitably R_d is hydrogen, a pharmaceutically acceptable cation, aroyl or a C_{1-10} alkanoyl group.

Suitably R_e is a 1,3-dioxyalkylene group of the formula $-O-(CH_2)_s-O-$, wherein s is 1 to 3, preferably s is 2 yielding a 1,3-dioxyethylene moiety, or ketal functionality.

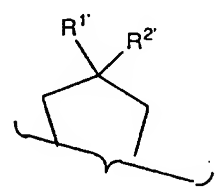
Suitably $R_{6'}$ is $NR_{19'}R_{20'}$; C_{1-6} alkyl; halosubstituted C_{1-6} alkyl; hydroxy substituted C_{1-6} alkyl; C_{2-6} alkenyl; or an aryl or heteroaryl optionally substituted by halogen, C_{1-6} alkyl, halosubstituted C_{1-6} alkyl, hydroxyl, or C_{1-6} alkoxy.

Suitably $R_{19'}$ is H or C_{1-6} alkyl.

Suitably $R_{20'}$ is H, C_{1-6} alkyl, aryl, benzyl, heteroaryl, C_{1-6} alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, C_{1-12} alkyl, C_{1-6} alkoxy, halosubstituted C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, or C_{1-6} alkylsulfinyl; or $R_{19'}$ and $R_{20'}$ may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members of the ring may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen. The ring may be saturated or contain more than one unsaturated bond. Preferably $R_{6'}$ is $NR_{19'}R_{20'}$ and $R_{19'}$ and $R_{20'}$ are preferably hydrogen.

When the R_2 cycloalkyl moiety is substituted by a NR_7R_{17} group, or NR_7R_{17} C_{1-10} alkyl group, and the R_7 and R_{17} are as defined in Formula (I), the substituent is preferably an amino, amino alkyl, or an optionally substituted pyrrolidinyl moiety.

A preferred ring placement on the cycloalkyl moiety is the 4-position, such as in a C_6 ring. When the cycloalkyl ring is di-substituted it is preferably di-substituted at the 4 position, such as in:



wherein $R^{1'}$ and $R^{2'}$ are independently the optional substituents indicated above for R_2. Preferably, $R^{1'}$ and $R^{2'}$ are hydrogen, hydroxy, alkyl, substituted alkyl, optionally substituted alkyne, aryl, arylalkyl, NR_7R_{17}, and $N(R_{10})C(O)R_{11}$. Suitably, the alkyl is a C_{1-4} alkyl, such as methyl, ethyl, or isopropyl; NR_7R_{17} and NR_7R_{17} alkyl, such as amino, methylamino, aminomethyl, aminoethyl; substituted alkyl such as in cyanomethyl, cyanoethyl, nitroethyl, pyrrolidinyl; aryl such as in phenyl; arylalkyl, such as in benzyl;

optionally substituted alkyne, such as ethyne or propynyl; or together $R^{1'}$ and $R^{2'}$ are a keto functionality.

Preferably R_4 is an optionally substituted phenyl; R_1 is an optionally substituted 4-pyridyl or 4-pyrimidinyl; and R_2 is an optionally substituted heterocyclyl, heterocyclyl C_{1-4} alkyl, a cycloalkyl or a cycloalkyl alkyl. More preferably R_2 is an optionally substituted C_4 or C_6 cycloalkyl, cyclopropyl methyl, morpholinyl butyl, morpholinyl propyl, morpholinyl ethyl, cyclohexyl substituted by methyl, phenyl, benzyl, amino, acetamide, aminomethyl, aminoethyl, cyanomethyl, cyanoethyl, hydroxy, nitroethyl, pyrrolidinyl, ethynyl, 1-propynyl, =O, -O-$(CH_2)_2$O-, =NOR_{11}, wherein R_{11} is hydrogen, alkyl or aryl, NHOH, or N(OH)-C(O)-NH_2; or R_2 is morpholinyl propyl, aminopropyl, piperidinyl, N-benzyl-4-piperidinyl, N-methyl-4-piperidinyl, 2,2,6,6-tetramethypiperidinyl, substituted piperidine, such as 1-formyl-4-piperidine, or a 1-ethoxycarbonyl-4-piperidine. More preferably R_1 is a 4-pyridyl or 4-pyrimidinyl subtituted by Y, NHRa, or C_{1-4} alkoxy.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in OR_3, or for certain R_2 moieties.

As used herein, "optionally substituted", unless specifically defined, shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10} alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; S(O)m alkyl, wherein m is 0, 1 or 2, such as methylthio, methylsulfinyl or methylsulfonyl; amino, mono and di-C_{1-10} alkyl substituted amino, NR_7R_{17} wherein the R_7R_{17} may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, mono and di- C_{1-10} alkyl substituted amino, such as in the NR_7R_{17} group; C_{1-10} alkyl; or halosubstituted alkyl, such as CF_3.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be

formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

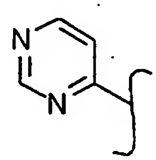
The following terms, as used herein, refer to:

- "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one double bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.
- The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroarylalkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclyl" (on its own or in any combination, such as "heterocyclylalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, or imidazolidine.
- The term "aralkyl" or "heteroarylalkyl" or "heterocyclylalkyl" is used herein to mean C_{1-4} alkyl as defined above attached to an aryl, heteroaryl or heterocyclyl moiety as also defined herein unless otherwise indicated.
- "sulfinyl" - the oxide S(O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

• "aroyl" - a C(O)Ar, wherein Ar is a phenyl, naphthyl, or aryl alkyl derivative such as defined above, such groups include but are not limited to benzyl and phenethyl.

• "alkanoyl" - a C(O)C_{1-10} alkyl wherein the alkyl is as defined above.

For the purposes herein the "core" 4-pyrimidinyl moiety for R_1 or R_2 is referred to as the formula:



It is recognized that the compounds for use in the present invention may exist as stereoisomers, regioisomers, or diastereiomers. These compounds may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

As noted previously, methods of making these compounds can be found in their respective patent applications as noted above.

Specifically exemplified compounds of Formula (I) include:

1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Chloropropyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Azidopropyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Aminopropyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Methylsulfonamidopropyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(N-Phenylmethyl)aminopropyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(N-Phenylmethyl-N-methyl)aminopropyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(1-Pyrrolidinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Diethylaminopropyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(1-Piperidinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(Methylthio)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[2-(4-Morpholinyl)ethyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(4-Morpholinyl)propyl]-4-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
(+/-)-1-[3-(4-Morpholinyl)propyl]-4-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
1-[3-(N-Methyl-N-benzyl)aminopropyl]-4-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
1-[3-(N-Methyl-N-benzyl)aminopropyl]-4-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

1-[4-(Methylthio)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[4-(Methylsulfinyl)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(Methylthio)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
(+/-)-1-[3-(Methylsulfinyl)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[2-(Methylthio)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[2-(Methylsulfinyl)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[4-(4-Morpholinyl)butyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-Cyclopropyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-Isopropyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-Cyclopropylmethyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-tert-Butyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(2,2-Diethoxyethyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-Formylmethyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-Hydroxyiminylmethyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-Cyanomethyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(4-Morpholinyl)propyl)-4-(4-fluorophenyl)-5-(2-methylpyridin-4-yl)imidazole;
4-(4-Fluorophenyl)-1-[3-(4-morpholinyl)propyl]-5-(2-chloropyridin-4-yl)imidazole;
4-(4-Fluorophenyl)-1-[3-(4-morpholinyl)propyl]-5-(2-amino-4-pyridyl)imidazole;
1-(4-Carboxymethyl)propyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(4-Carboxypropyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Carboxymethyl)ethyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(3-Carboxy)ethyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
1-(1-Benzylpiperidin-4-yl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[3-(4-morpholinyl)propyl]imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-benzylpiperidin-4-yl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(2-propyl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(cyclopropylmethyl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-carboxyethyl-4-piperidinyl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
1-Methyl-4-phenyl-5-(4-pyridyl)imidazole;
1-Methyl-4-(3-chlorophenyl)-5-(4-pyridinyl)imidazole;
1-Methyl-4-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
(+/-)-1-Methyl-4-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
(+/-)-4-(4-Fluorophenyl)-1-[3-(methylsulfinyl)propyl]-5-(4-pyridinyl)imidazole;
4-(4-Fluorophenyl)-1-[(3-methylsulfonyl)propyl]-5-(4-pyridinyl)imidazole;
1-(3-Phenoxypropyl)-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;

1-[3-(Phenylthio)propyl]-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-quinolyl)imidazole;
(+/-)-1-(3-Phenylsulfinylpropyl)-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
1-(3-Ethoxypropyl)-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
1-(3-Phenylsulfonylpropyl-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
1-[3-(4-Morpholinyl)propyl]-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole;
1-[3-(4-Morpholinyl)propyl]-4-(3,4-dichlorophenyl)-5-(4-pyridyl)imidazole;
4-[4-(4-Fluorophenyl)-1-[3-(4-morpholinyl)propyl]-5-(pyrimid-2-one-4-yl)imidazole;
4-(4-Fluorophenyl)-5-[2-(methylthio)-4-pyrimidinyl]-1-[3-(4-morpholinyl)propyl]-imidazole;
(+/-)-4-(4-Fluorophenyl)-5-[2-(methylsulfinyl)-4-pyrimidinyl]-1-[3-(4-morpholinyl)-propyl]imidazole;
(E)-1-(1-Propenyl)-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
1-(2-Propenyl)-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
5-[(2-N,N-Dimethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-[3-(4-morpholinyl)-propyl]imidazole;
1-[3-(4-Morpholinyl)propyl]-5-(4-pyridinyl)-4-[4-(trifluoromethyl)phenyl]imidazole;
1-[3-(4-Morpholinyl)propyl]-5-(4-pyridinyl)-4-[3-(trifluoromethyl)phenyl]imidazole;
1-(Cyclopropylmethyl)-4-(3,4-dichlorophenyl)-5-(4-pyridinyl)imidazole;
1-(Cyclopropylmethyl)-4-(3-trifluoromethylphenyl)-5-(4-pyridinyl)imidazole;
1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-(2-methylpyrid-4-yl)imidazole;
1-[3-(4-Morpholinyl)propyl]-5-(4-pyridinyl)-4-(3,5-bistrifluoromethylphenyl)-imidazole;
5-[4-(2-Aminopyrimidinyl)]-4-(4-fluorophenyl)-1-(2-carboxy-2,2-dimethylethyl)imidazole;
1-(1-Formyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(4-pyridinyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)imidazole;
1-(2,2-Dimethyl-3-morpholin-4-yl)propyl-4-(4-fluorophenyl)-5-(2-amino-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(4-pyridyl)-1-(2-acetoxyethyl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-benzylpyrrolin-3-yl)imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethylpiperidin-4-yl)imidazole;
5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-N-methylpiperidine)-imidazole;
5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-N-morpholino-1-propyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole;
5-[(2-Ethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;
4-(4-Fluorophenyl)-5-[2-(isopropyl)aminopyrimidiny-4-yl]-1-(1-methylpiperidin-4-yl)imidazole;
5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-N-morpholino-1-propyl)-imidazole;
5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)imidazole;
5-[4-(2-N-Methylthio)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole;
4-(Fluorophenyl)-1-(methyl-4-piperidinyl)-5-(2-methylthio-4-pyrimidinyl)imidazole;
4-(Fluorophenyl)-1-(methyl-4-piperidinyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;
1-tert-Butyl-4-(4-fluorophenyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;
5-[4-(2-Aminopyrimidinyl)]-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-4-piperidinyl)imidazole;
5-[4-(2-N-Methylamino-4-pyrimidinyl)]-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-4-piperidine)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-thiopyranyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-pyranyl)imidazole;
5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(2-cyanoethyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfinylpyranyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfonylpyranyl)-imidazole;
5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(2,2,2-trifluoroethyl-4-piperidinyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(trifluoroacetyl-4-piperidinyl)-imidazole;
5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxy carbonyl-4-piperidinyl)imidazole;
4-(4-Fluorophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-5-(2-methoxy-pyrimidin-4-yl)imidazole;
4-(4-Fluorophenyl)-5-(2-methylthio-pyrimidin-4-yl)imidazole;
5-[(2-Benzylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;
4-(4-Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-[2-(4-tetrahydrothio-pyranyl)aminopyrimidin-4-yl]imidazole;
5-[(2-(3-Chlorobenzylamino))pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methyl-piperidin-4-yl)imidazole;

5-[(2-(1-Naphthylmethylamino))pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[(2-(1-Benzyl-4-piperidinylamino))pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[2-[3-(morpholino)propyl]-aminopyrimidiny-4-yl]imidazole;

5-[2-[(3-Bromophenyl)amino]pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[(2-(Piperonylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[(2-(4-Piperdinylamino))pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[(2-(5-Chlorotryptamino))pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[(2-(2,2,6,6-Tetramethylpiperidin-4-yl)amino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[(2-(1-Ethoxycarbonyl))piperdin-4-yl]aminopyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole;

5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole;

5-[4-(2-Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)-imidazole;

4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[(2-phenylamino)pyrimidin-4-yl]-imidazole;

4-(4-Fluorophenyl)-1-(2,2,6,6-tetramethylpiperidin-4-yl)-5-[(2-phenylamino)pyrimidin-4-yl]imidazole;

4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[2-[3-(imidazol-1-yl)propyl]aminopyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperidin-4-yl]imidazole;

4-(4-Fluorophenyl)-5-[2-[3-(imidazol-1-yl)propyl]aminopyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole;

4-(4-Thiomethylphenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(1-ethoxy carbonylpiperidin-4-yl)imidazole;

4-(4-Thiomethylphenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Methylsulfinylphenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(4-fluorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3-fluorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(2-fluorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(4-benzyloxyphenyl)amino)pyrimidin-4-yl]-1-(1-ethoxycarbonylpiperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3-benzyloxyphenyl)amino)pyrimidin-4-yl]-1-(1-ethoxycarbonylpiperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3-trifluoromethylphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3,4-difluorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(4-hydroxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3-hydroxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(4-methoxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3-methoxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(2-methoxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

4-(4-Fluorophenyl)-5-[(2-(3-fluoro-2-methylphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole;

1-(4-Oxocyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole;

cis -1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole;

trans-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole;

1-(4-Oxocyclohexyl)-4-(4-fluorophenyl)-5-[(2-methylthio)pyrimidin-4-yl]-imidazole;

trans-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methylthio)pyrimidin-4-yl]imidazole;

1-(4-Oxocyclohexyl)-4-(4-fluorophenyl)-5-[(2-hydroxy)pyrimidin-4-yl]imidazole;

1-(4-Oxocyclohexyl)-4-(4-fluorophenyl)-5-[(2-isopropoxy)pyrimidin-4-

yl]imidazole;

1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-isopropoxy)pyrimidin-4-yl]imidazole;

trans-1-(4-Hydroxy-4-methylcyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)-pyrimidin-4-yl]imidazole;

cis-1-(4-Hydroxy-4-methylcyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)-pyrimidin-4-yl]imidazole;

trans-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-ethoxy)pyrimidine-4-yl]imidazole;

1-Cycloheptyl-4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazole;

1-Cyclopropyl-4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazole;

1-Cyclobutyl-4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazole;

1-Cyclopentyl-4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazole;

1-Cyclohexyl-4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazole;

trans-5-[4-(2-Methoxy)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(2-tetrahydropyranyl)-oxycyclohexyl]imidazole;

1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-hydroxy)pyrimidin-4-yl]imidazole

cis-1-[(4-Hydroxy-4-methylcyclohexyl)]-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole;

trans-1-[(4-Hydroxy-4-methylcyclohexyl)]-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole;

trans-1-(4-Aminocyclohexyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole;

trans-4-(4-Fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]-1-[4-((methylthio)methoxy)cyclohexyl]imidazole;

cis-1-(4-Aminocyclohexyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole;

trans-1-[(4-Butyryloxy)cyclohexyl]-4-(4-fluorophenyl)-5-[(2-methoxypyrimidin)-4-yl]imidazole;

trans-4-(4-Fluorophenyl)-1-[4-(2-(N,N-dimethylamino)ethoxy)cyclohexyl]-5-[(2-methoxy)pyrimidin-4-yl]imidazole hydrochloride;

cis/trans-1-(4-Hydroxy-4-hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxypyridin-4-yl)imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)pyridin-4-yl]imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyridin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)pyrimidin-4-yl]-imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-aminocarbonylphenoxy)pyrimidin-4-yl]-imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-ethylphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-benzyloxyphenoxy)pyrimidin-4-yl]-imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-cyanophenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-hydroxyphenoxy)pyrimidin-4-yl]imidazole;
1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[2-(phenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyridin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyridin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyridin-4-yl]imidazole;
1-[3-(N-Morpholino)propyl]-4-(4-fluorophenyl)-5-[2-(phenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-methoxyphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-phenylphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-phenoxyphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-hydroxyphenoxy)pyrimidin-4-yl]imidazole;
1-(3-(N-Morpholino)propyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2-hydroxyphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-methylenedioxyphenoxy)-pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2-fluorophenoxy)pyrimidin-4-

yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2-methoxyphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-difluorophenoxy)pyrimidin-4-yl]imidazole;
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylsulfonylphenoxy)pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-thiophenoxypyrimidin-4-yl)imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(1-methyltetrazol-5-ylthio)pyridin-4-yl]imidazole
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(2-acetamidophenoxy)pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(3-propionamidophenoxy)pyrimidin-4-yl]imidazole;
1-Cyclohexyl-4-(4-fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2-methylphenoxy)pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethyl-4-chlorophenoxy)-pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(indol-4-yloxy)pyrimidin-4-yl]imidazole;
1-Cyclopropyl-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole;
1-Isopropyl-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole;
1-Cyclopentyl-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole;
(+/-)-1-(1-Hydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)-imidazole;
3-[4-(4-Fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazol-1-yl]propionitrile;
(R)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl)imidazole;
(S)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl)imidazole;
(+/-)-1-(1-Phenoxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)-imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylacetamido)phenoxy-pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamidophenoxy)-pyrimidin-4-yl]imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-isopropoxy-4-pyrimidinyl)imidazole;
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole;
5-(2-Hydroxy-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-(2-Methoxy-4-pyridinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-(2-*iso*-Propoxy-4-pyridinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-methyl-4-piperidinyl]imidazole;
5-(2-Ethoxy-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
1-(1-Ethylcarboxylpiperidin-4-yl)-3-(4-thiomethylphenyl)-5-[2-(thiomethyl)-pyrimidin-4-yl]imidazole;
1-(1-Ethylcarbonylpiperidin-4-yl)-4-(4-methylsulfinylphenyl)-5-[2-methylsulfinyl-pyrimidin-4-yl]imidazole; or
pharmaceutically acceptable salts thereof.

METHODS OF TREATMENT

The cytokine inhibitor compounds, in particular those of Formula (I) or a pharmaceutically acceptable salt, can be used in the manufacture of a medicament for the prophylactic treatment or management of excessive, undesired or inappropriate uterine activity in a mammal, preferably a human, which activity is exacerbated or caused by excessive or unregulated cytokine production by such mammal.

The cytokine inhibitors of the p38/CSPB pathway are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF.

The cytokine inhibitors of the p38/CSPB pathway are administered in an amount sufficient to inhibit the cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some cases to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event; or

d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells, however, also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor beta (TNF-ß).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

The MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physiochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as IL-1 and TNF. The cytokine biosynthesis inhibitors for use in the present invention, for instance compounds of Formula (I), have been determined to be potent and selective inhibitors of this CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages. The CSBP protein is described in detail in Patent Application USSN 08/123175 Lee et al., filed September 1993;

Lee et al., PCT/US94/10529 filed 16 September 1994; USSN 08/605002, filed 15 April 1996; USSN 08/469421, USSN 08/468902; and Lee et al., *Nature* 300, n(**72**), 739-746 (Dec. 1994). Inhibitors of the variants and homologs of the CSBP protein are also considered as another aspect of the present invention. One such variant is the p38 beta protein, as described in Jiang, Y., et al., J. Biol. Chem., 271, pp 17920-26 (1996); and variants in USSN 08/746788, filed 15 November 1996; whose disclosures are incorporated by reference in their entirety herein.

Intracellular signal transduction is the means by which cells respond to extracellular stimuli. Regardless of the nature of the cell surface receptor (e.g. protein tyrosine kinase or seven-transmembrane G-protein coupled), protein kinases and phosphatases along with phopholipases are the essential machinery by which the signal is further transmitted within the cell [Marshall, J. C. Cell , **80**, 179-278 (1995)]. Protein kinases can be categorized into five classes with the two major classes being, tyrosine kinases and serine / threonine kinases depending upon whether the enzyme phosphorylates its substrate(s) on specific tyrosine(s) or serine / threonine(s) residues [Hunter, T., Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T.; Sefton, B. M.; eds. vol. 200, Academic Press; San Diego, 1991].

For most biological responses, multiple intracellular kinases are involved and an individual kinase can be involved in more than one signaling event. These kinases are often cytosolic and can translocate to the nucleus or the ribosomes where they can affect transcriptional and translational events, respectively. The involvement of kinases in transcriptional control is presently much better understood than their effect on translation as illustrated by the studies on growth factor induced signal transduction involving MAP/ERK kinase [Marshall, C. J. Cell , **80**, 179 (1995); Herskowitz, I. Cell, **80**, 187 (1995); Hunter, T. Cell , **80**, 225 (1995); Seger, R., and Krebs, E. G. FASEB J., 726-735 (1995)].

While many signaling pathways are part of cell homeostasis, numerous cytokines (e.g., IL-1 and TNF) and certain other mediators of inflammation (e.g., COX-2, and iNOS) are produced only as a response to stress signals such as bacterial lippopolysaccharide (LPS). The first indications suggesting that the signal transduction pathway leading to LPS-induced cytokine biosynthesis involved protein kinases came from studies of Weinstein [Weinstein, *et al.*, J. Immunol. **151**, 3829(1993)] but the specific protein kinases involved were not identified. Working from a similar perspective, Han [Han, *et al.*, Science, **265**, 808(1994)] identified murine p38 as a kinase which is tyrosine phosphorylated in response to LPS. Definitive proof of the involvement of the p38 kinase in LPS-stimulated signal transduction pathway leading to the initiation of proinflammatory cytokine

biosynthesis was provided by the independent discovery of p38 kinase by Lee [Lee; *et al.*, Nature, **372**, 739(1994)] as the molecular target for a novel class of anti-inflammatory agents. The discovery of p38 (termed by Lee as CSBP 1 and 2) provided a mechanism of action of a class of anti-inflammatory compounds for which SK&F 86002 was the prototypic example. These compounds inhibited IL-1 and TNF synthesis in human monocytes at concentrations in the low uM range [Lee, *et al.*, Int. J. Immunopharmac. 10(7), 835(1988)] and exhibited activity in animal models which are refractory to cyclooxygenase inhibitors [Lee; *et al.*, Annals N. Y. Acad. Sci., **696**, 149(1993)].

MITOGEN AND STRESS ACTIVATED PROTEIN KINASE CASCADES

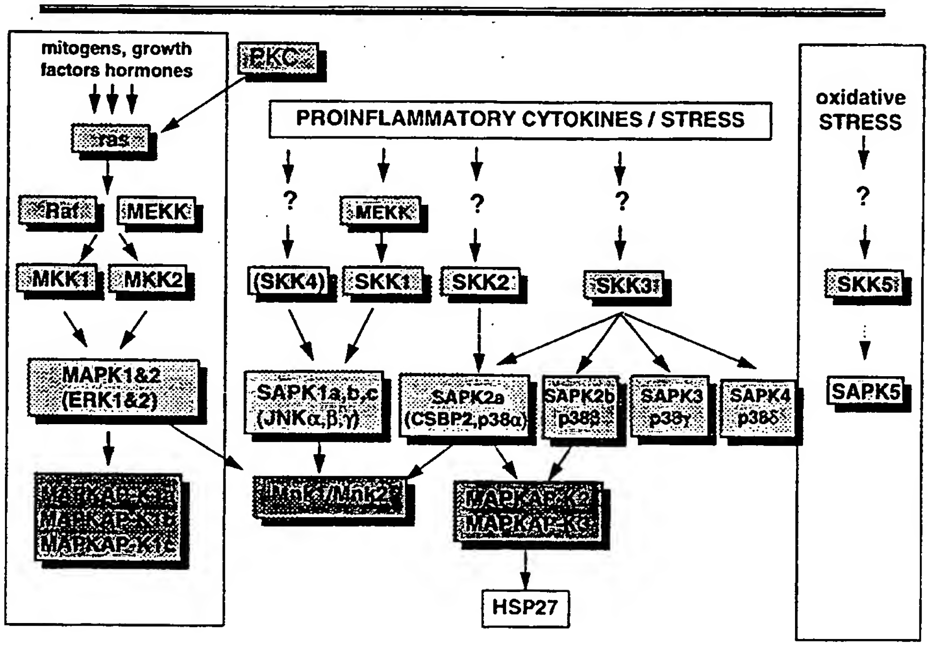


Figure 1

It is now firmly established that CSBP/p38 is a one of several kinases involved in a stress-response signal transduction pathway which is parallel to and largely independent of the analogous mitogen-activated protein kinase (MAP) kinase cascade (Figure 1). Stress signals, including LPS, pro-inflammatory cytokines, oxidants, UV light and osmotic stress, activate kinases upstream from CSBP/p38 which in turn phosphorylate CSBP/p38 at threonine 180 and tyrosine 182 resulting in CSBP/p38 activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/p38 which in turn phosphorylate heat shock protein Hsp 27 (Figure 2). It is not yet known whether MAPKAP-2, MAPKAP-3, Mnk1 or Mnk2 are involved in cytokine biosynthesis or alternatively that inhibitors of

CSBP/p38 kinase might regulate cytokine biosynthesis by blocking a yet unidentified substrate downstream from CSBP/p38 [Cohen, P. Trends Cell Biol., 353-361(1997)].

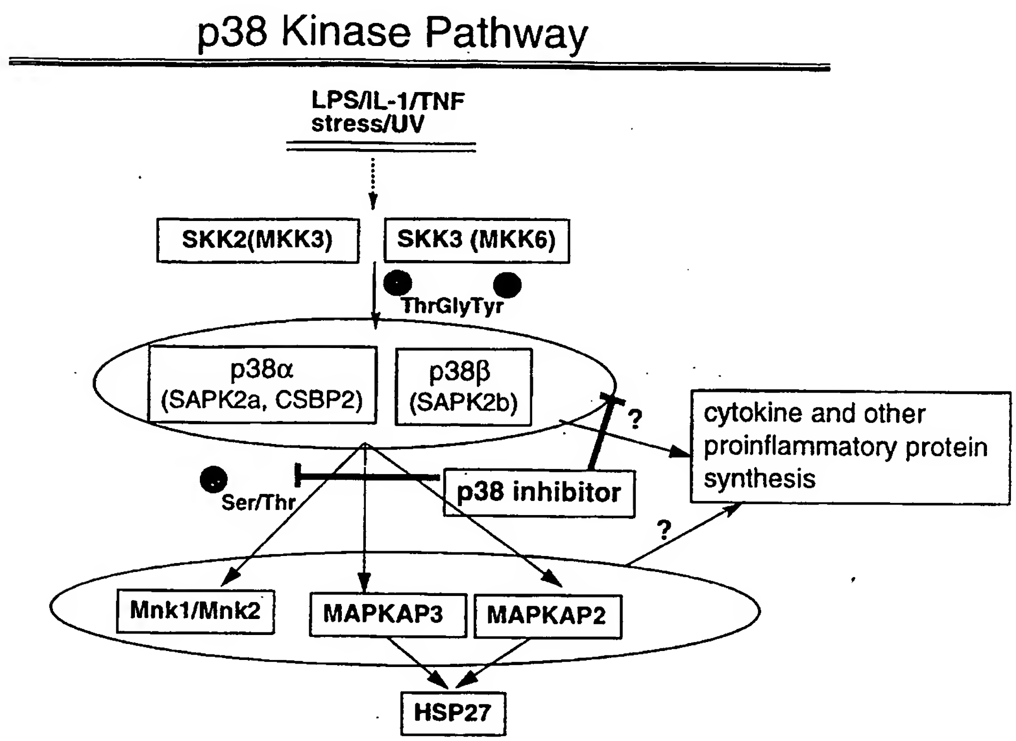


Figure 2

What is known, however, is that in addition to inhibiting IL-1 and TNF, CSBP/p38 kinase inhibitors (SK&F 86002 and SB 203580) also decrease the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF and COX-2. Inhibitors of CSBP/p38 kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that CSBP/p38 is involved not only cytokine synthesis, but also in cytokine signaling [CSBP/P38 kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].

Pharamaceutical Formulations

The cytokine biosynthesis inhibitors for use in the present invention will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice, for example they will be formulated with a pharmaceutically

acceptable diluent or carrier. Cytokine biosynthesis inhibitors, and pharmaceutically acceptable salts thereof, and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The cytokine biosynthesis inhibitors may be administered in conventional dosage forms prepared by combining a cytokine biosynthesis inhibitor with standard pharmaceutical carriers according to conventional procedures. Cytokine biosynthesis inhibitors may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The cytokine biosynthesis inhibitors may be administered topically, that is by non-systemic administration. This includes the application of an inhibitor externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from

0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably include a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

The cytokine biosynthesis inhibitors may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. The cytokine biosynthesis inhibitors may

also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the cytokine biosynthesis inhibitors, including compounds of Formula (I), the preferred, dosage regimen would be parenteral until contractions cease, and then as long as necessary to optimise fetal well-being prior to delivery, i.e. as near to term (37 weeks gestation) as is necessary. In light of this, daily parenteral dosage regimen will be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily topical dosage regimen, such as may be applied to prevent cervical ripening, could be administered topically to the cervix to prevent cervical softening and delay fetal membrane rupture. Such as topical dosage will preferably be in a formulation containing from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen, if applicable, will preferably be from about 0.01 mg/kg to about 1 mg/kg per day.

It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of cytokine biosynthesis inhibitor will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds for use in the present invention, such as those noted above, may be determined by the following *in vitro* assays:

Assays for Interleukin-1 (IL-1), Interleukin-8 (IL-8), and Tumour Necrosis Factor (TNF) are well known in the art, and may be found in a number of publications, and patents. Representative suitable assays for use herein are described in Adams et al., US 5,593,992, whose disclosure is incorporated by reference in its entirety.

Interleukin - 1 (IL-1)

Human peripheral blood monocytes are isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the

procedure of Colotta *et al*, J Immunol, **132**, 936 (1984). These monocytes (1×10^6) are plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells are allowed to adhere for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds are then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures are incubated at 37°C for an additional 24h. At the end of this period, culture supernatants are removed and clarified of cells and all debris. Culture supernatants are then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, **84**, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, **6** (1), 1-12 (1990) (ELISA assay).

In vivo TNF assay:

(1) Griswold *et al.*, Drugs Under Exp. and Clinical Res.,XIX (6), 243-248 (1993); or

(2) Boehm, *et al.*, *Journal Of Medicinal Chemistry* 39, 3929-3937 (1996) whose disclosures are incorporated by reference herein in their entirety.

LPS-induced TNFα Production in Mice and Rats

In order to evaluate in vivo inhibition of LPS-induced TNFα production in rodents, both mice and rats are injected with LPS.

Mouse Method

Male Balb/c mice from Charles River Laboratories are pretreated (30 minutes) with compound or vehicle. After the 30 min. pretreat time, the mice are given LPS (lipopolysaccharide from Esherichia coli Serotype 055-85, Sigma Chemical Co., St Louis, MO) 25 ug/mouse in 25 ul phosphate buffered saline (pH 7.0) intraperitoneally. Two hours later the mice are killed by CO_2 inhalation and blood samples are collected by exsanguination into heparinized blood collection tubes and stored on ice. The blood samples are centrifuged and the plasma collected and stored at –20°C until assayed for TNFα by ELISA.

Rat Method

Male Lewis rats from Charles River Laboratories are pretreated at various times with compound or vehicle. After a determined pretreat time, the rats are given LPS (lipopolysaccharide from Esherichia coli Serotype 055-85, Sigma Chemical Co., St Louis, MO) 3.0 mg/kg intraperitoneally. The rats are killed by CO_2 inhalation and heparinized whole blood is collected from each rat by cardiac

puncture 90 minutes after the LPS injection. The blood samples are centrifuged and the plasma collected for analysis by ELISA for TNFα levels.

ELISA Method

TNFα levels were measured using a sandwich ELISA, as described in Olivera et al., Circ. Shock, 37, 301-306, (1992), whose disclosure is incorporated by reference in its entirety herein, using a hamster monoclonal antimurine TNFα (Genzyme, Boston, MA) as the capture antibody and a polyclonal rabbit antimurine TNFa (Genzyme) as the second antibody. For detection, a peroxidase-conjugated goat antirabbit antibody (Pierce, Rockford, IL) was added, followed by a substrate for peroxidase (1 mg/ml orthophenylenediamine with 1% urea peroxide). TNFα levels in the plasma samples from each animal were calculated from a standard curve generated with recombinant murine TNFα (Genzyme).

LPS-Stimulated Cytokine Production in Human Whole Blood

Assay: Test compound concentrations were prepared at 10 X concentrations and LPS prepared at 1 ug/ml (final conc. of 50 ng/ml LPS) and added in 50 uL volumes to 1.5 mL eppendorf tubes. Heparinized human whole blood was obtained from healthy volunteers and was dispensed into eppendorf tubes containing compounds and LPS in 0.4 mL volumes and the tubes incubated at 37 C. Following a 4 hour incubation, the tubes were centrifuged at 5000 rpm for 5 minutes in a TOMY microfuge, plasma was withdrawn and frozen at -80 C.

Cytokine measurement: IL-I and/or TNF were quantified using a standardized ELISA technology. An in-house ELISA kit was used to detect human IL-1 and TNF. Concentrations of IL-1 or TNF were determined from standard curves of the appropriate cytokine and IC50 values for test compound (concentration that inhibited 50% of LPS-stimulated cytokine production) were calculated by linear regression analysis.

Cytokine Specific Binding Protein Assay

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine

inhibitor binding assay was developed using soluble cystosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee et al., filed September 1993, US 5,783,644 and US 5,777,097 Lee et al., WO94/10529 filed 16 September 1994 and Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

CSBP/p38 Kinase Assay:

This assay measures the CSBP/p38-catalyzed transfer of ^{32}P from [a-^{32}P]ATP to threonine residue in an epidermal growth factor receptor (EGFR)-derived peptide (T669) with the following sequence: KRELVEPL*T*PSGEAPNQALLR (residues 661-681). (See Gallagher *et al.*, "Regulation of Stress Induced Cytokine Production by Pyridinyl Imidazoles: Inhibition of CSBP Kinase", BioOrganic & Medicinal Chemistry, 1997, 5, 49-64).

Reactions were carried in round bottom 96 well plate (from Corning) in a 30 ml volume. Reactions contained (in final concentration): 25 mM Hepes, pH7.5; 8 mM $MgCl_2$; 0.17 mM ATP (the $Km_{[ATP]}$ of p38 (see Lee et al., Nature 300, n72 pg 639-746 (Dec. 1994)); 2.5 uCi of [g-32P]ATP; 0.2 mM sodium orthovanadate; 1 mM DTT; 0.1% BSA; 10% glycerol; 0.67 mM T669 peptide; and 2-4 nM of yeast-expressed, activated and purified p38. Reactions were initiated by the addition of [gamma-32P]Mg/ATP, and incubated for 25 min. at 37 °C. Inhibitors (dissolved in DMSO) were incubated with the reaction mixture on ice for 30 minutes prior to adding the 32P-ATP. Final DMSO concentration was 0.16%. Reactions were terminated by adding 10 ul of 0.3 M phosphoric acid, and phosphorylated peptide was isolated from the reactions by capturing it on p81 phosphocellulose filters. Filters were washed with 75 mM phosphoric acids, and incorporated 32P was quantified using beta scintillation counter. Under these conditions, the specific activity of p38 was 400-450 pmol/pmol enzyme, and the activity was linear for up to

2 hr of incubation. The kinase activity values were obtained after subtracting values generated in the absence of substrate which were 10-15% of total values.

Modulation of PGE_2 and IL-1β production

The Examples below determine the effects of the CSAID™ compounds on the ability to modulate both PGE_2 and IL-1β production from fetal membranes.

Fetal membranes were obtained from term elective caesarean sections from uncomplicated pregnancies and washed in phosphate buffered saline containing 10% penicillin, streptomycin and L-glutamine. Whole membrane discs consisting of adherent amnion and chorio-decidua each measuring 1.5 cm were then cut and incubated overnight in multiwell tissue culture plates at 37°C, 95% air, 5% CO_2 in serum free medium 199 (Sigma) supplemented with insulin, transferrin and selenium. Following the addition of fresh medium 199 four experimental groups (A to D) were set up. Each experimental group consisted of identical triplicate tissue culture wells.

Group	Medium
A	Control (Unstimulated)
B	Control (Unstimulated) + SKF86002
C	LPS
D	LPS + SKF 86002

LPS (Sigma-E.coli Serotype 0114:B4) was used at a concentration of 10^{-8} g/dl. SKF 86002 was dissolved in ethanol to provide a final concentration of 10 μM. Group A consisted of control discs incubated in medium alone. Incubations were carried out for four, eight and twelve hours following which the supernatants were harvested and stored at -20°C for subsequent estimation of IL-1β and PGE_2 levels by ELISA {enzyme linked immunosorbent assay (Amersham)}.

Control wells consisting of ethanol and medium 199 with and without LPS were also included. Fetal membrance viability was assessed using the diaphorase histochemical method, see Aldred L.F., et al. (1983) *J. Steroid Biochem.*, **18**, 411-414.

<u>**RESULTS: IL-1β production:**</u>

Mixed model analysis of variance was used to analyse the data. The assumptions of the analysis of variance were checked and a log transformation was found to be the most appropriate. Data is presented on an untransformed original scale for ease of interpretation.

Group:

Group A v Group B $p=0.007$
Difference = 25.5 95% CI (-2.3, 53.3)

Group C v Group D $p=0.002$
Difference 45.5 95% CI (17.9, 73.2)

Time:

4 hours v 12 hours $p=0.08$
Difference 22.7 95% CI (-3.0, 48.4)

PGE_2 production:

Mixed model analysis of variance was used to analyse the data. The assumptions of the analysis of variance were checked and a log transformation was found to be the most appropriate. Data is presented on an untransformed scale for ease of interpretation.

Group:

Group A v Group B $p<0.001$
Difference 109 95% CI (78.96, 139.9)

Group C v Group D $p<0.001$
Difference 161 95% CI (130.6, 191.9)

Tissue viability was not compromised by the addition of the drug as tested by the diaphorase method. Ethanol alone did not significantly inhibit production of either PGE_2 or IL-1β from the fetal membranes.

Conclusions

The results indicate that following treatment with the prototype CSAID™ compound SKF 86002 [6-(4-fluorophenyl)-2,3-dihydro-5-(4-

pyridinyl)imidazo[2,1-b]thiazole] there was a significant decrease in the production of both PGE_2 and IL-1β from fetal membranes.

SKF 86002 reduced IL-1β production from both control ($p=0.07$) and LPS stimulated wells ($p=0.002$). The effects of the agent appeared to diminish after 12 hours incubation. Maximal production of IL-1β from all treatment groups occurred after 8 hours incubation. IL-1β production was significantly lower at 12 hours compared to 4 hours in all treatment groups ($p=0.08$). SKF86002 reduced PGE_2 production from both control ($p<0.001$) and LPS stimulated wells ($p<0.001$). The effects did not seem to diminish throughout the incubation period.

This data indicates that CSAID™ compounds have utility to modulate prostaglandin and interleukin production from gestational tissues. As the compound decreased basal PGE_2 and IL-1β production as well as production in response to LPS, this provides a basis for treatment of both infection driven and idiopathic pre-term labour.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of prophylactic treatment or management of excessive, undesired or inappropriate uterine activity in a mammal, which method comprises administering to said mammal an effective amount of a compound which inhibits the production, transcription or translation of a cytokine.

2. The method according to Claim 1 wherein the cytokine is inhibited by inhibition of the kinase CSBP/p38/RK.

3. The method according to Claim 1 or 2 wherein the uterine activity is pre-term labour which is infection driven.

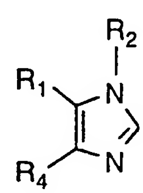
4. The method according to Claim 1 or 2 wherein the uterine activity is idiopathic pre-term labour.

5. The method according to Claim 1 or 2 wherein the uterine activity is unwanted dilatation, or ripening of the cervix.

6. The method according to Claim 1 or 2 wherein the uterine activity is preterm rupture of the fetal membrane.

7. The method according to Claim 1 or 2 wherein the uterine activity is eclampsia or pre-eclampsia.

8. The method according to any one of the preceding claims wherein the compound is of the formula (I):



(I)

wherein:

R_1 is a pyrid-4-yl, pyrimidin-4-yl, pyridazin-4-yl, 1,2,4-triazin-5-yl, quinol-4-yl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl ring, which ring is optionally substituted independently one to three times with Y, NHR_a, optionally substituted C_{1-4} alkyl, halogen, hydroxyl, optionally substituted C_{1-4} alkoxy,

optionally substituted C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or $N(R_{10})C(O)R_b$;

Y is O-R_a;

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $C(Z)NR_7R_{17}$, $C(Z)OR_{16}$, $(CR_{10}R_{20})_vCOR_{12}$, SR_5, SOR_5, OR_{12}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $ZC(Z)R_{12}$, $NR_{10}C(Z)R_{16}$, or $(CR_{10}R_{20})_vNR_{10}R_{20}$, and which, for other positions of substitution, is halogen, cyano, $C(Z)NR_{13}R_{14}$, $C(Z)OR_3$, $(CR_{10}R_{20})_{m''}COR_3$, $S(O)_mR_3$, OR_3, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_3$, $NR_{10}S(O)_{m'}R_8$, $NR_{10}S(O)_{m'}NR_7R_{17}$, $ZC(Z)R_3$ or $(CR_{10}R_{20})_{m''}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

m is 0, or an integer having a value of 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is hydrogen, $(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenylC_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaryl alkyl, heterocyclyl and heterocyclyl alkyl groups may be optionally substituted;

Z is oxygen or sulfur;

R_a is a C_{1-6} alkyl, aryl, arylC_{1-6} alkyl, heterocyclyl, heterocyclylC_{1-6} alkyl, heteroaryl, or heteroarylC_{1-6} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties SR_5 being SNR_7R_{17} and SOR_5 being SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is a C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, or $(CR_{10}R_{20})_nNR_{13}R_{14}$ moiety; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl moieties may be optionally substituted;

R_9 is hydrogen, $C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted arylC_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen and C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclylC_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted arylC_{1-4} alkyl, or together with the nitrogen to which they are attached R_{13} and R_{14} form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylC_{1-10} alkyl, heterocyclyl, heterocyclylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

9. The method according to Claim 8 wherein R_1 is optionally substituted 4-pyridyl or 4-pyrimindyl.

10. The method according to Claim 8 or 9 wherein R_a is alkyl, aryl, arylalkyl, halosubstituted arylalkyl, halosubstituted aryl, heterocyclyl alkyl, hydroxyalkyl, alkyl-1-piperidine-carboxylate, heterocyclyl, alkyl substituted heterocyclyl, halosubstituted heterocyclyl, or aryl substituted heterocyclyl.

11. The method according to Claim 10 wherein R_a is methyl, ethyl, iospropoxy, benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, morpholinopropyl, 2-hydroxyethyl, ethyl-1-piperidinecarboxylate, piperonyl, piperidin-4-yl, alkyl substituted piperidine, chlorotryptamine, or tetrathiohydropyranyl.

12. The method according to any one of claims 8 to 11 wherein R_4 is optionally substituted phenyl.

13. The method according to Claim 12 wherein the phenyl is substituted in the 4-position by halogen.

14. The method according to any one of claims 8 to 13 wherein R_2 is selected from optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nNS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, aryl$C_{1-10}$ alkyl, $(CR_{10}R_{20})_nNR_{13}R_{14}$, optionally substituted C_{3-7} cycloalkyl, and optionally substituted C_{3-7} cycloalkylC_{1-10} alkyl.

15. The method according to Claim 14 wherein R_2 is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-aminopiperidine, 4-amino-2,2,6,6-tetramethyl piperidine, 4-hydroxycyclohexyl, 4-methyl-4-hydroxycyclohexyl, 4-pyrrolinindylcyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-ketocyclohexyl, 4-oxiranyl, or 4-hydroxy-4-(1-propynyl)cyclohexyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/03015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/44 A61K31/505 A61K31/445 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHWALISZ K ET AL: "Cervical ripening with the cytokines interleukin 8, interleukin 1 beta and tumour necrosis factor alpha in guinea-pigs." HUMAN REPRODUCTION, (1994 NOV) 9 (11) 2173-81. JOURNAL CODE: HRP. ISSN: 0268-1161., XP002094115 ENGLAND: United Kingdom	1,3-6
Y	see the whole document ---	2,8-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1999	05/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	ERNY R ET AL: "The effects of oral administration of progesterone for premature labor." AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1986 MAR) 154 (3) 525-9. JOURNAL CODE: 3NI. ISSN: 0002-9378., XP002094116 United States see the whole document	1,3,4
X	MIZUTANI S ET AL: "Positive effect of estradiol and progesterone in severe pre-eclampsia." EXPERIMENTAL AND CLINICAL ENDOCRINOLOGY, (1988 DEC) 92 (2) 161-70. JOURNAL CODE: EPA. ISSN: 0232-7384., XP002094117 GERMANY, EAST: German Democratic Republic see the whole document	1,7
X	WO 95 07699 A (COLUMBIA LAB INC) 23 March 1995 see page 1, line 1 - line 16	1,3,4,7
A	ITO A ET AL: "Suppression of interleukin 8 production by progesterone in rabbit uterine cervix." BIOCHEMICAL JOURNAL, (1994 JUL 1) 301 (PT 1) 183-6. JOURNAL CODE: 9YO. ISSN: 0264-6021., XP002094118 ENGLAND: United Kingdom see the whole document	1,3,4,7
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Y	see the whole document	2,8-15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BRY K ET AL: "Transforming growth factor-beta opposes the stimulatory effects of interleukin -1 and tumor necrosis factor on amnion cell prostaglandin E2 production: implication for preterm labor." AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1992 JUL) 167 (1) 222-6. JOURNAL CODE: 3NI. ISSN: 0002-9378., XP002094120 United States see the whole document ---	2,8-15
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Y	GALLAGHER T F ET AL: "Regulation of stress -induced cytokine production by pyridinylimidazoles;inhibition of CSBP kinase." BIOORGANIC AND MEDICINAL CHEMISTRY, (1997 JAN) 5 (1) 49-64. JOURNAL CODE: B38. ISSN: 0968-0896., XP002094123 ENGLAND: United Kingdom see the whole document ---	2,8-15
Y	WO 97 25045 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY L (US); BOEHM JEFFREY C (US);) 17 July 1997 see abstract; claims; examples see page 31, line 1 - line 7 ---	2,8-15

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INTERNATIONAL SEARCH REPORT

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 40143 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY LEROY (US); GALLAGHER TIMOTHY) 19 December 1996 see abstract see page 50, line 14 - line 25; claims; examples	2,8-15
Y	WO 96 21654 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY LEROY (US); GARIGIPATI RAVI S) 18 July 1996 see abstract see page 35, line 18 - page 36, line 2; claims; examples	2,8-15
Y	WO 96 21452 A (ADAMS JERRY LEROY ;BOEHM JEFFREY CHARLES (US); GALLAGHER TIMOTHY F) 18 July 1996 see abstract see page 37, line 4 - line 10; claims; examples	2,8-15
Y	WO 95 02591 A (SHELDRAKE PETER WILLIAM ;ADAMS JERRY LEROY (US); BOEHM JEFFREY CHA) 26 January 1995 see abstract; claims; examples	2,8-15
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ernational Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 26278 A (STEENO RES GROUP AS ;GESSER BORBALA (DK); GROENHOEJ LARSEN CHRISTI) 24 July 1997 see abstract see page 1, line 1 - line 25; claims; table 3 ---	1,3,4
X	WO 95 22546 A (CELL THERAPEUTICS INC) 24 August 1995 see abstract see page 10, line 23 - line 38; claims ---	1,3,4
A	WALKER, RICHARD F. ET AL: "Ovarian effects of an anti-inflammatory-immunomodulatory drug in the rat" TOXICOL. APPL. PHARMACOL. (1988), 94(2), 266-75 CODEN: TXAPA9;ISSN: 0041-008X, XP002094124 see the whole document -----	1-7

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/03015

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-15
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the the large number of compounds which are theoretically contained within the definition "compound which inhibits the production, transcription or translation of a cytokine" of claim 1 and which are defined by the general formula of claim 8, the search has to be restricted on economic grounds. The search was limited to the general idea of the invention, to the compounds mentioned in claim 8 wherein R1 is 4-pyridyl or 4-pyrimidinyl and to the compound mentioned in the examples (Art.6 PCT; Guidelines Chapt.II.7 last sentence and Chapt.III,3.7). Claim searched completely: 9

Claims searched incompletely: 1-8,10-15

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PCT/GB 98/03015

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